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Martine J. Sealy[1,2], Tanadech Dechaphunkul[3,4], Cees P. van der Schans[1,5,6,], Wim P. Krijnen[1,7], Jan L.N. Roodenburg[2], John Walker[3], Harriët Jager-Wittenaar[1,2], Vickie E. Baracos[3]

Affiliations

[1] Research Group Healthy Ageing, Allied Health Care and Nursing, Hanze University of Applied Sciences, Petrus Driessenstraat 3, 9714 CA, Groningen, The Netherlands. E-mail: m.j.sealy@pl.hanze.nl, ha.jager@pl.hanze.nl, w.p.krijnen@pl.hanze.nl, c.p.van.der.schans@pl.hanze.nl

[2] Department of Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. E-mail: j.l.n.roodenburg@umcg.nl

[3] Department of Oncology, University of Alberta, Edmonton, AB, Canada. E-mail: john.Walker2@albertahealthservices.ca, vickie.baracos@ualberta.ca

[4] Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Prince of Songkla University, Hatyai, Songkhla, Thailand, 90110. E-mail: tonmee034@hotmail.com

[5] Department of Rehabilitation Medicine, University of Groningen, University Medical Center, Groningen, The Netherlands. E-mail: c.p.van.der.schans@pl.hanze.nl

[6] Department of Health Psychology Research, University of Groningen, University Medical Center, Groningen, The Netherlands. E-mail: c.p.van.der.schans@pl.hanze.nl

[7] Johan Bernoulli Institute for Mathematics and Computer Science, University of Groningen, Groningen, The Netherlands. E-mail: w.p.krijnen@pl.hanze.nl

Corresponding author: Martine J. Sealy

A Hanze University of Applied Sciences, School of Health Care Studies

Petrus Driessenstraat 3, 9714 CE Groningen, The Netherlands

T +31 (0)50-595 3604 | **E** m.j.sealy@pl.hanze.nl

ABSTRACT

Background and aims: We studied whether low pre-treatment muscle mass, measured with CT at thoracic (T4) or lumbar level (L3) associates with early termination of chemotherapy related to toxicity in head and neck cancer (HNC) patients.

Methods: This was a retrospective chart and image review. Adult HNC patients treated with (surgery and) platinum-based chemo-radiotherapy were included if a pre-treatment CT scan at T4 or L3 level was available. Muscle mass was evaluated by assessment of skeletal muscle index (SMI; cm^2/m^2). T4 and L3 SMI measurements were corrected for deviation from their respective means and were merged into one score for SMI difference (cm^2/m^2). All cases were assessed for presence of toxicity-related unplanned early termination of chemotherapy ('early termination'). Univariate and multivariate logistic regression models were used to investigate associations between pooled SMI and early termination.

Results: 213 patients (age: 57.9±10.3 y, male: 77%, T4 image: 45%) were included. A significant association between SMI as a continuous variable and early termination was found, both in the univariate analysis (p=0.007, OR=0.96 [0.94-0.99]) and the multivariate analysis (p=0.021, OR 0.96 [0.92-0.99]). The multivariate models identified potential associations with type of chemotherapy, presence of co-morbidity, a combination of (former) smoking and alcohol consumption, and sex.

Conclusion: Lower muscle mass was robustly associated with higher odds of early termination of chemotherapy in HNC patients. Further prospective studies are required to tailor the care for patients with low muscle mass and to avoid early termination of chemotherapy.

Keywords

Computed Tomography; Muscle mass; Body composition; Chemotherapy; Treatment toxicity; Head and neck cancer

Abbreviations

HNC = head and neck cancer

CT = computed tomography

CRT = concomitant radiotherapy and chemotherapy treatment

SxCRT = concomitant radiotherapy and chemotherapy treatment with prior surgery

T4 = 4th thoracic vertebra

L3 = 3th lumbar vertebra

ECOG performance status = Eastern Cooperative Oncology Group performance status

BMI = body mass index

SMA = skeletal muscle area

SMI = skeletal muscle index

SCAD = Smoothly Clipped Absolute Deviation

AIC = minimum Akaike Information Criterion

BIC = minimizing Bayesian Information Criterion

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INTRODUCTION

Decreased oral intake due to tumor location cancer treatment, and/or cachexia is common in patients with head and neck cancer (HNC) and may induce loss of skeletal muscle [1-4]. In turn, low muscle mass has a negative impact on overall function and survival in patients with HNC [5-9]. However, the treatment approach in patients with locally advanced HNC can be aggressive and may consist of surgery followed by radiotherapy, with or without concomitant chemotherapy. In patients not eligible for surgery or when the anticipated functional outcome with surgery is poor, radiotherapy with concomitant chemotherapy is preferred [10-12]. Although prognosis improves when patients are capable of completing their therapy, early termination of treatment related to toxicity is observed more often in cancer patients with low muscle mass, and thus such benefit may be limited [7,13,14].

The development of chemotherapy toxicity may be partially explained by variation in body composition in patients with cancer [15]. The overall weight is comprised mostly of fat tissue and non-fat tissue. In turn, non-fat tissue is comprised of bone tissue and lean tissue such as organ tissues (e.g., liver and kidneys) and muscle tissue [16,17]. Distribution and metabolism of water soluble chemotherapy agents, such as cisplatin, mainly takes place in the lean tissue [18]. Therefore, patients with low muscle mass may have a smaller amount of area available for distribution of chemotherapy agents due the limited amount of lean tissue. Recent studies have revealed there is considerable variation in the proportions of lean and fat tissues in patients with cancer, and patients with solid tumors may present as overweight or obese, while simultaneously showing severe loss of skeletal muscle mass [8,13,19]. Body area estimates based on body mass and stature are used for dose calculation of chemotherapy agents such as cisplatin [20]. Thus, if a chemotherapy agent distributes well in lean tissue, patients with relatively low muscle mass may be at risk of receiving a higher dose of

chemotherapy agent relative to the actual amount of lean tissue, due to overestimation of lean tissue. This relatively high dose of chemotherapy may increase risk of chemotherapy toxicity [7,14,17,21].

Chemotherapy toxicity may result in early termination of chemotherapy [22]. Accurate identification of patients with low muscle mass is currently possible, since muscle mass has become identifiable and quantifiable with image-based approaches, such as computed tomography (CT). CT analysis of the lumbar muscle area has been thoroughly validated for the evaluation of human body composition and correlates well with lean body mass [23-25]. In some patient populations, CT images of the lumbar muscle area are not generally available, and CT analysis of thoracic muscle area may serve as an alternative [26]. However, although it is now possible to accurately identify patients with low muscle mass, it is still unclear to what extent toxicity of chemotherapy treatment correlates with muscle area identified with lumbar or thoracic CT cross-sections in HNC patients. Therefore, we aimed to study whether low pre-treatment lumbar or thoracic muscle area as measured with CT is associated with toxicity-related early termination of chemotherapy treatment, in patients with HNC treated with concomitant radiotherapy and chemotherapy.

MATERIALS AND METHODS

Patients and study design

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional research ethics board. Data were collected in consecutive adult patients diagnosed with HNC during their initial visit to the outpatient medical oncology clinic at the tertiary cancer treatment center serving northern Alberta. Demographic information, and cancer site and stage were obtained from the Alberta Cancer Registry, certified by the North American Association for Central Cancer Registries. Cancer stage was based on the American Joint Committee on Cancer (7th Edition) stage groupings for HNC [27]. HNC tumor sites were based on the International Classification of Diseases for Oncology (ICD)-O-3 site codes. Cohorts were sampled from March 2004 until July 2010 (Sample I) and from May 2012 until May 2016 (Sample II). Adult patients diagnosed with HNC, mainly presenting cancer of the lip, oral cavity, nose, paranasal sinus, larynx, and pharynx, were considered for inclusion if they received concomitant radiotherapy and platinum-based chemotherapy treatment (CRT) with curative intent, with or without prior surgery (Sx). To be considered for inclusion, a routine diagnostic CT image taken before start of CRT including the 4^{th} thoracic vertebra (T4; sample I) or the 3^{th} lumbar vertebra (L3; sample II) needed to be available.

The primary treatment for advanced stages of HNC was CRT; in addition, approximately half of the patients in our cohort had prior HNC surgery, with tumor resection, bilateral neck dissection, and free flap reconstruction. Radiotherapy treatment included conventional or tomotherapy 66-76 cGy. The main treatment plans for chemotherapy were cisplatin 100 mg/m^2, three weekly (3 cycles), cisplatin 40 mg/ m^2, weekly (7 cycles), or, if cisplatin could not be tolerated, carboplatin 1.5 area under the curve (AUC) weekly (6-7 cycles). For each patient, chemotherapy type and dose were selected by the treating

oncologist. If patients had a contraindication to high dose cisplatin such as poor renal function or pre-existing hearing problems, carboplatin was used in the first instance.

Measures

Data collected from medical charts included: number of days between CT scan and start of chemotherapy and radiotherapy; type of treatment; presence of co-morbidities; performance status was recorded as Eastern Cooperative Oncology Group (ECOG) [28]; alcohol intake; history of smoking, treatment plan of platinum-based chemotherapy and chemotherapy toxicities.

Body composition

Weight and height were recorded according to standard procedures by hospital staff. Weight (kg) was measured with a medical balance beam scale and height (m) with a stadiometer. Body mass index (BMI) was calculated [weight (kg)/height (m^2)]. Percentage of weight loss in the last month before starting CRT was retrieved from Patient-Generated Subjective Global Assessment Short Form data [29], as collected in routine care. Body composition was assessed by evaluating (PET-)CT images that were taken for diagnostic purposes. Most studies using this approach have adopted the convention of quantifying muscle cross-sectional area in a single image landmarked at L3 [22-24,30]. However in HNC routine diagnostic imaging does not always include the abdominal region, thus we selected T4 as an alternative vertebral landmark for Sample I, as this region represents large and diverse muscle areas and was included in staging studies in the majority of patients. For Sample II, routine PET-CT imaging included L3 in the majority of patients.

One axial image at T4 or L3 was selected for analysis of total muscle cross-sectional area (cm^2) [23,31]. CT image parameters included: contrast-enhanced, 5 mm slice thickness, 120 kVp, and ~290 mA. Observers were blinded to the patients' treatment and toxicity status. Muscles were quantified within a Hounsfield unit range of −29 to +150 HU using Slice-O–Matic software (v.5.0; Tomovision, Magog, Canada). Total muscle cross-sectional area (SMA) was computed for each image. The directly determined unit for SMA was cm^2 of total T4 or L3 skeletal muscle. Cross-sectional area of total muscle at T4 or L3 were normalized for stature, and skeletal muscle index (SMI; cm^2/m^2) was calculated. Correction for deviation of the mean enables pooling of the SMI results of sample I and sample II, while allowing continued use of the original unit of measurement (cm^2/m^2). It could be performed because standard deviations of T4 and L3 measurements were similar (12.6 cm^2/m^2 and 10.3 cm^2/m^2, respectively). The mean SMI of Sample I was subtracted from all SMI measurements in Sample I (T4 measurements) and the mean SMI of Sample II was subtracted from all SMI measurements in Sample II (L3 measurements). After correction for deviation from the mean, the scores were combined in one pooled SMI variable representing the SMI deviation to the mean (cm^2/m^2).

Outcome measures

In this study, early termination of chemotherapy related to toxicity ('early termination') was considered the primary outcome measure and was defined as completion of at least one cycle of chemotherapy less than planned. If the initial chemotherapy treatment plan was altered from cisplatin to carboplatin (often due to ototoxicity), and cycles were completed, this was not considered an early termination. Otherwise, if early termination was specifically attributed to toxicity, early termination was considered present. Reduction of the dose of cisplatin or carboplatin provided all cycles where completed, was not considered early termination.

Statistical analysis

Mean (standard deviation; SD) or median scores (interquartile range; IQR) are reported for all continuous variables. Absolute numbers (percentages) are reported for ordinal and dichotomous variables. Differences between Sample I and Sample II were explored with Pearson Chi square, Mann-Whitney U test, or independent samples t-test.

Univariate analysis was used to test the association between pooled SMI and early termination. Multivariate binary logistic regression analyses were used to investigate possible effects of sex, age, BMI, presence of co-morbidities (present, not present); ECOG performance status (ECOG ≤1, ECOG>1), smoking (yes, no), alcohol consumption (yes, no), tumor site (oropharynx, other), treatment plan (CRT, SxCRT), and type of platin-based chemotherapy (cisplatin, carboplatin) on early termination. Since multivariate modeling based on exclusion of variables as a result of their univariate performance (for instance excluding all variables with a p-value ≥0.10) may result in overlooking possible interactions in the multivariate analysis, all variables included in the univariate model were also included in the multivariate analysis, regardless of univariate performance. Due to the large number of variables, three model selection procedures were explored to identify associations. As a primary model selection procedure, the penalized regression approach according to the Smoothly Clipped Absolute Deviation (SCAD) [32] penalty was used, as it performs well in variable selection without creating bias [33,34].For selecting the explanatory variables, the value of the penalty parameter is determined by repeating the cross-validation procedure 200 times and taking the mean from these repeats. To test the robustness of the results, the model resulting from SCAD was compared with that obtained from minimum Akaike Information Criterion (AIC) [35] and minimizing Bayesian Information Criterion (BIC) [36] approaches. To allow for analysis of all included patients, missing data were imputed by the Multivariate

Imputation by Chained Equations procedure for the variables alcohol intake (n=2) and ECOG performance status (n=13) [37,38].

Furthermore, to provide insight in the relation between SMI, one month weight loss and early termination, we presented distribution of percentage weight loss in one month across SMI stratified for early termination being absent or present, and tested for mean differences with univariate binary logistic regression analysis and for differences in proportions with Fisher's exact test. Finally, toxicity profiles of cisplatin-based chemotherapy treatment may differ from carboplatin-based treatment. Therefore, difference in distribution of SMI (cm^2/m^2) stratified for early termination being absent or present was tested for cisplatin and carboplatin separately with an independent samples Mann-Whitney U test. The association between muscle mass and early termination was explored with univariate binary logistic regression, for subgroups treated with cisplatin or carboplatin separately.

In the analyses, a p-level of <0.05 was considered significant and Odds Ratios (OR) [95% CI] were presented. Descriptive, univariate and explorative analyses were performed with SPSS (version 24.0 2016, IBM Inc., Chicago, Il). Multivariate analysis was performed with R (R version 3.4.1, R Core Team Vienna, 2017).

RESULTS

In total, 213 patients met the inclusion criteria and could be included in the analysis (Sample I: n=93; Sample II: n=120). Characteristics of the included HNC patients prior to CRT are reported in Table 1. All patients received at least one cycle of chemotherapy. Of these 213 patients, 61 (29%) terminated chemotherapy prematurely. In one patient that terminated chemotherapy early, the initial chemotherapy treatment plan was altered from cisplatin to carboplatin. In 28 patients, the initial chemotherapy treatment plan was altered from cisplatin to carboplatin, and treatment was considered completed. The following reasons for early termination of chemotherapy treatment were not considered toxicity-related: non-completion due to non-compliance (n=4); further chemotherapy treatment not indicated (n=2); non-completion of CRT due to reported radiation-related side effects (n=2); postponement of treatment due to surgical infections (n=1) or personal circumstances (n=1). Dose reduction of chemotherapy treatment ranged from 25% to 90% and occurred in 19 patients. Seven of these patients had toxicity-related dose reductions preceding early termination, and early termination was considered present. In eight patients the reason for dose reduction was not described and all cycles were completed, and early termination was not considered present. Finally, in four patients dose reductions were related to chemotherapy toxicity, but all cycles were completed, and early termination was not considered present.

Body composition measurements

In Sample I, CT images at T4 level of 93 eligible patients were analyzed. In sample II, CT images at L3 level were available in 120 of 124 (94.4%) eligible HNC patients. All selected images could be analyzed and SMI was calculated. Pre-treatment anthropometrical measurements and indices of body composition of the participants are presented in Table 2.

Patients that altered their treatment from cisplatin to carboplatin did not have a significantly different pooled SMI when compared to patients continuously treated with cisplatin ($p=0.823$), or when compared to all other patients ($p=0.541$). Frequency of early termination did not significantly differ between patients treated with cisplatin 100 mg/m^2 and cisplatin 40 mg/m^2 ($p=0.864$). The univariate and multivariate modeling analysis of pooled SMI and early termination corrected for possible confounding variables in HNC patients is presented in Table 3. In addition to pooled SMI, variables that emerged associated with early termination were sex, type of chemotherapy, co-morbidity and (former) smoking combined with alcohol consumption. The time interval between CT and CRT was significantly different for Sample I and Sample II ($p<0.001$). To rule out possible effect modification, the time interval between CT and CRT (days) was therefore added to the statistical modeling analyses. However, time interval between CT and CRT was not identified as effect modifier of pooled SMI on early termination in the AIC, BIC, or SCAT model. Associated odds of early termination of chemotherapy treatment across the distribution of pooled SMI in HNC patients are presented in Figure 1.

Percentage one month weight loss was significantly associated with early termination ($p<0.001$). Additionally, interaction between SMI and early termination appeared different depending on the level of one month weight loss and vice versa, indicating SMI and one month weight loss may modify each other's effects on early termination. Since the focus was on the association between SMI and early termination, weight loss was not included in the primary analysis. Instead, the association between SMI and percentage one month weight loss across SMI stratified for early termination is presented separately in Figure 2.

Figure 3 illustrates the distribution of SMI stratified by absence or presence of early termination of chemotherapy for cisplatin-based and carboplatin-based treatment in patients with head and neck cancer. To further explore the association between muscle mass and early

termination for the different types of chemotherapy agents, a sub-analysis was performed for the cisplatin and the carboplatin subgroup, respectively. The sub-analysis showed that in the cisplatin subgroup, a higher SMI was significantly associated with a lower incidence of early termination (p=0.025; OR 0.96 [95% CI: 0.93-1.00]). This indicates that if SMI is 1 cm^2/m^2 higher, the odds of early termination decrease with 4% in the patients treated with cisplatin. Also in the carboplatin subgroup, a higher SMI was significantly associated with a lower incidence of early termination (p=0.041; OR 0.93 [95% CI: 0.86-1.00]). This indicates that if SMI is 1 cm^2/m^2 higher, the odds of early termination decrease with 7% in the patients treated with carboplatin.

DISCUSSION

The results of our study indicate that cross-sectional measurements of large and representative muscle areas are significantly associated with incidence of toxicity-related early termination of chemotherapy in patients with HNC. A lower level of lumbar and thoracic SMI of 1 cm^2/m^2 was firmly associated with 4 to 5% higher odds of early termination of chemotherapy. Conversely, a higher level of lumbar and thoracic SMI of 1 cm^2/m^2 was firmly associated with 4 to 5% lower odds of early termination of chemotherapy. In our population, one month weight loss was significantly associated with early termination and modified the effect of SMI, and vice versa. Patients with SMI below mean and weight loss showed significantly higher changes of early termination of treatment. Co-variables that were selected in one or more models of the multivariate analysis were type of chemotherapy, presence of co-morbidity, alcohol consumption, smoking, combined alcohol consumption and smoking, and sex. Of these variables, type of chemotherapy, presence of co-morbidity, and combined alcohol consumption and smoking were significantly associated with early termination in one or more models of the multivariate analysis.

The results of this study agree with other studies that have shown that cancer patients with low muscle mass generally are vulnerable to chemotherapy toxicity [6,15,21,39]. We speculate that this could be partially explained by higher concentrations of water soluble chemotherapy agents such as cisplatin and, to a lesser extent, carboplatin in lean tissues in patients with low muscle mass [18]. Our exploratory results also indicate that for both cisplatin-based and carboplatin-based chemotherapy, lower muscle mass was associated with a significantly higher incidence of early termination. Alternatively, complications of chemotherapy may also be explained by reduced overall function as a result of low muscle mass. Studies show that cancer patients with low muscle mass are also vulnerable to a range

of other problems, such as slower recovery, complications from surgery, and shorter survival [5,40-42].

Availability of abdominal CT images was better than reported in other studies in HNC patients [43, 44]. Whereas in Sample I (2004-2010), diagnostic CT images of head and chest were standard practice in head and neck cancer patients, in Sample II (2012-2016), a 94% availability of L3 level CT measurements was encountered. This broad availability of abdominal CT images can be explained by the implementation of routine imaging with whole body PET-CT scans in the more recent Sample II. Although in recent years a growing number of HNC patients have whole body PET-CT scans for staging purposes, routine abdominal imaging is currently not part of NCCN guidelines, and clinical practice varies per country and institution [32]. As long as not all CT cross-sectional areas are as well-validated as L3, before deciding on analyzing thoracic or cervical muscle areas in HNC patients, we recommend to first explore the availability of whole body PET-CT scans, and thus L3 images.

To our knowledge, our study is the first to include CT cross-sections of large and representative lumbar and thoracic muscle areas in head and neck cancer patients. The results of our advanced statistical analysis confirmed the results of a study that explored the association between CT cross-sections of smaller cervical muscle areas and toxicity-related early termination in HNC patients [44]. Additionally, our study identified possible interactions of SMI and early termination with type of chemotherapy regimen, presence of co-morbidity, and combined smoking and alcohol consumption.

Our study also had some limitations. Firstly, we were not able to acquire CT images that included cross-sections of L3 vertebra for all patients. Currently, a validated formula is available for cross-sectional muscle area at L3 level, [25] but not for T4 level. Therefore, lean body mass on the whole body level could not be estimated. However, we were able to pool

and interpret results by correcting T4 and L3 measurements for deviation to their means. Secondly, type and dose of chemotherapy were significantly different between Sample I (2004-2010) and Sample II (2012-2016). This difference resulted from adaptations in head and neck cancer treatment guidelines, in which use of carboplatin is nowadays less often recommended and use of the lower dose of cisplatin is more often recommended. As a result, the subgroup of patients treated with weekly cisplatin (40 mg/m^2) in our sample was limited (n=34). However, toxicity-related early termination did not significantly differ between the subgroup of patients treated with high dose cisplatin 100 mg/m^2 and those treated with weekly cisplatin 40 mg/m^2. Also, studies indicate that high-dose cisplatin at 100 mg/m^2 and weekly cisplatin at 40 mg/m^2 have similar cumulative dose and toxicity profiles [45-47]. Hence, we considered it justified to dichotomize type of chemotherapy treatment into cisplatin versus carboplatin in the multivariate analysis. Finally, we combined the data of patients with CRT and surgery prior to CRT. Patients with surgery prior to CRT may have a different disease profile than patients that did not have surgery prior to CRT [12]. Therefore, we included presence or absence of surgery as a co-variable in our statistical analysis. This statistical analysis showed no significant difference in early termination of treatment for both groups.

Chemotherapy (e.g. cisplatin) has important radiosensitizing capacities and patients with HNC treated with concomitant chemotherapy and radiotherapy have high survival [48]. For cisplatin dose, response studies suggest that a cumulative dose of >200 mg/m2 is needed for survival benefit of chemotherapy [46,47]. This will not be achieved if treatment is terminated early. Since incidence of early termination is higher in patients with lower muscle mass, the odds of treatment completion may improve if patients receive chemotherapy treatment that is tailored to their muscle mass or lean body mass instead of whole body area estimates. Further prospective studies are required to develop a dosing strategy that will be tolerated by patients with lower muscle mass and avoid early termination. Also, adjusting

chemotherapy dosage to prevent toxicity should not be considered without testing possible effects of adjustments on disease control.

Additionally, our study was a retrospective study, and thus some covariables could not be studied in great detail. Therefore, in future studies on muscle mass and chemotherapy toxicity in patients with HNC, we recommend taking into account more in-depth analyses of covariables such as weight loss, type of chemotherapy, presence of co-morbidity, and combined smoking and alcohol consumption and sex. These variables may possibly interact with chemotherapy toxicity. For instance, the relationship between low muscle mass and weight loss combined and early termination of chemotherapy treatment needs further study. Further, presence of co-morbidity could be explored with more attention for severity of co-morbidities (for instance by implementing the Charlson co-morbidity index). Finally, the association between (combined) drinking and smoking and SMI needs further exploration, and the association between combined drinking and smoking and early termination of chemotherapy treatment could be further explored by stratifying for quantities of alcohol intake and smoking.

In conclusion, in this study we found that a lower muscle mass is associated with higher odds of toxicity-related early termination of chemotherapy treatment in patients with HNC. Further prospective studies are required to tailor the care for patients with low muscle mass and to avoid early termination of chemotherapy.

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Legends to Figures

Figure 1. Associated odds of early termination of chemotherapy treatment for skeletal muscle index (SMI; cm^2/m^2) in patients with head and neck cancer.

Figure 2. Distribution of 1 month weight loss percentage across absence (cross) or presence (circle) for early termination of chemotherapy for skeletal muscle index corrected for deviation of the mean (SMI: cm2/m2) in patients with head and neck cancer.

Figure 3. Distribution of skeletal muscle index corrected for deviation of the mean (SMI: cm^2/m^2) across absence (left) or presence (right) of early termination of chemotherapy for cisplatin-based and carboplatin-based treatment in patients with head and neck cancer.

Table 1. Characteristics of patients with head and neck cancer prior to chemo-radiotherapy treatment reported for the whole study sample and separately for Sample I and II

Basic characteristic	**Total N=213**	**Sample I N=93**	**Sample II N=120**	**(Mean) diff p value**
Age (years)				
Mean ± SD	57.9±10.3	58.0 (10.7)	57.8 (10.1)	0.842
Sex				
Male (%)	164 (77.0)	71 (76.3)	93 (77.5)	0.858
Tumor site				
Oral cavity	31 (14.6)	9 (9.7)	22 (18.3)	0.155
Pharynx	144 (67.6)	67 (72.1)	77 (64.2)	
Larynx	22 (10.3)	12 (12.9)	10 (8.3)	
Other	16 (7.5)	5 (5.4)	11 (9.2)	
Stage (%)				
1	2 (0.9)	0	2 (1.7)	0.602
2	6 (2.8)	2 (2.2)	4 (3.3)	
3	27 (12.7)	12 (12.9)	15 (12.5)	
4	171 (80.3)	76 (81.7)	95 (79.2)	
X	7 (3.3)	3 (3.2)	4 (3.3)	
Tumor classification				
T1	32 (15.0)	12 (12.9)	20 (16.7)	0.158
T2	53 (24.9)	22 (23.7)	31 (25.8)	
T3	58 (27.2)	28 (30.1)	30 (25.0)	
T4	54 (25.4)	28 (30.1)	26 (21.7)	
Tx	16 (7.5)	3 (3.2)	13 (10.8)	
Mode of treatment				
Primary chemo-radiotherapy (CRT)	105 (49.3)	49 (52.7)	56 (46.7)	0.383
Surgery plus post-operative chemo-radiotherapy (Sx-CRT)	108 (50.7)	44 (47.3)	64 (53.3)	
Time between CT and CRT (days)				
Median (interquartile range)	55.0 (27.0-93.0)	32.0 (15.0-82.5)	70.0 (42.5-103.0)	<0.001*
Type and dose of chemotherapy				
- Cisplatin 100 mg/m2	133 (62.4)	59 (63.4)	74 (61.7)	<0.001*
- Cisplatin 40 mg/m2	34 (16.0)	3 (3.2)	31 (25.8)	
- Carboplatin 1.5 AUC	46 (21.6)	31 (33.3)	15 (12.5)	
ECOG performance status (%)				
0. Normal	99 (46.5)	48 (56.1)	51 (42.5)	0.148
1. Not normal self	71 (33.3)	25 (26.9)	46 (38.3)	
2. Not feeling up to most	19 (8.9)	7 (7.5)	12 (10.0)	
3. Little activity	11 (5.2)	5 (5.4)	6 (5.0)	
4. Bed ridden				
Missing	13 (6.1)	8 (8.6)	5 (4.2)	
Presence of co-morbidity				
Yes (%)	126 (59.2)	53 (57.0)	73 (60.3)	0.571

Significance set at a 0.05 level

Table 1. continued

Basic characteristic	Total N=213	Sample I N=93	Sample II N=120	(Mean) diff p value
Smoking				
Never (%)	49 (23.0)	19 (20.2)	30 (25.4)	0.509
Former (%)	86 (40.4)	37 (39.4)	48 (40.7)	
Current (%)	77 (36.2)	38 (40.4)	39 (33.1)	
Unknown (%)	1 (0.5)		1 (0.8)	
History of alcohol drinking				
Yes (%)	140 (65.7)	61 (65.6)	79 (65.8)	0.836
No (%)	71 (33.3)	32 (34.4)	39 (32.5)	
Unknown (%)	2 (0.9)		2 (1.7)	
Early termination of chemotherapy related to toxicity				
Present (%)	61 (28.6)	23 (24.7)	38 (31.7)	0.267

Significance set at a 0.05 level

Table 2

Table 2. Anthropometrics and indices of body composition of head and neck cancer patients prior to chemo-radiotherapy treatment

Body composition measurements	**Total N=213**	**Sample I[a] N=93**	**Sample II[b] N=120**	**(mean) diff Sample I and II, p-value**
Body weight Mean ± SD				
Overall kg	77.8±18.5	75.3±17.8	79.7±18.8	0.083
Male kg	81.3±17.6	78.9±17.9	83.1±17.3	
Female kg	65.9±16.3	63.4±11.2	68.0±19.5	
(mean) difference male and female, p-value	<0.001*	<0.001*	<0.001*	
Weight loss in 1 month[c] Mean ± SD				
Overall %	1.46±3.56	1.06±3.72	1.76±3.42	0.159
Male %	1.37±3.39	1.19±3.76	1.50±3.09	
Female %	1.78±4.12	0.65±3.65	2.65±4.32	
(mean) difference male and female, p-value	0.489	0.565	0.126	
Body mass index Mean ± SD				
Overall (m^2)	26.3±5.4	25.9±5.0	26.6±5.7	0.315
Male (m^2)	26.6±5.2	26.9±5.3	26.2±5.1	
Female (m^2)	25.5±5.9	25.8±6.9	25.0±4.7	
(mean) difference male and female, p-value	0.209	0.353	0.397	
Skeletal muscle area Mean ± SD				
Overall (cm^2)		191.27 (46.36)	155.44 (36.86)	
Male (cm^2)		208.92 (36.50)	168.2 (30.6)	
Female (cm^2)		134.32 (22.91)	111.07 (23.23)	
(mean) difference male and female, p-value		<0.001*	<0.001*	
Skeletal muscle index Mean ± SD				
Overall (cm^2/m^2)		65.53 (12.60)	51.62 (10.16)	
Male (cm^2/m^2)		69.45 (11.02)	53.4 (9.4)	
Female (cm^2/m^2)		52.88 (8.41)	42.23 (7.79)	
(mean) difference male and female, p-value		<0.001*	<0.001*	

*Significance set at a 0.05 level

[a] Sample I: 4th thoracic vertebra (T4) as vertebral landmark.

[b] Sample II: 3th lumbar vertebra (L3) as vertebral landmark.

[c] Percentage of weight loss in one month reported at intake for chemo-radiotherapy.

Table 3

Table 3. Univariate and multivariate modeling analysis of skeletal muscle index and toxicity-related early termination of chemotherapy treatment corrected for possible confounding variables in HNC patients

	Early termination of chemotherapy related to toxicity							
	Univariate (n=213)		Multivariate (n=213)					
Covariables	**OR [95%CI]**	**p-value**	**AIC OR [95% CI]**	**p-value**	**BIC OR [95%CI]**	**p-value**	**SCAD OR [95%]**	**p-value**
Skeletal muscle index (cm^2/m^2)[a]	0.96 [0.94-0.99]	0.007[b]	0.95 [0.92-0.98]	0.001[b]	0.96 [0.93-0.99]	0.004[b]	0.96 [0.92-0.99]	0.021[b]
Body mass index (BMI; kg/m^2)	0.97 [0.92-1.03]	0.277						
Age (years)	1.02 [0.99-1.06]	0.126						
Sex (Male)								
Female	2.33 [1.19-4.54]	0.013[b]					1.36 [0.59-3.08]	0.469
Stage (I&II)								
III&IV	1.21 [0.24-6.19]	0.817						
Tumor site (Others)								
Oropharynx	0.67 [0.36-1.24]	0.203						
Treatment (CRT)								
Sx+CRT	1.33 [0.73-2.41]	0.353						
Chemotherapy (Cisplatin)								
Carboplatin	0.54 [0.24-1.20]	0.128	0.36 [0.14-0.84]	0.023[b]	0.35 [0.14-0.79]	0.017[b]	0.38 [0.15-0.87]	0.029[b]
Time between CT and CRT (days)	1.00 [0.99-1.01]	0.598						

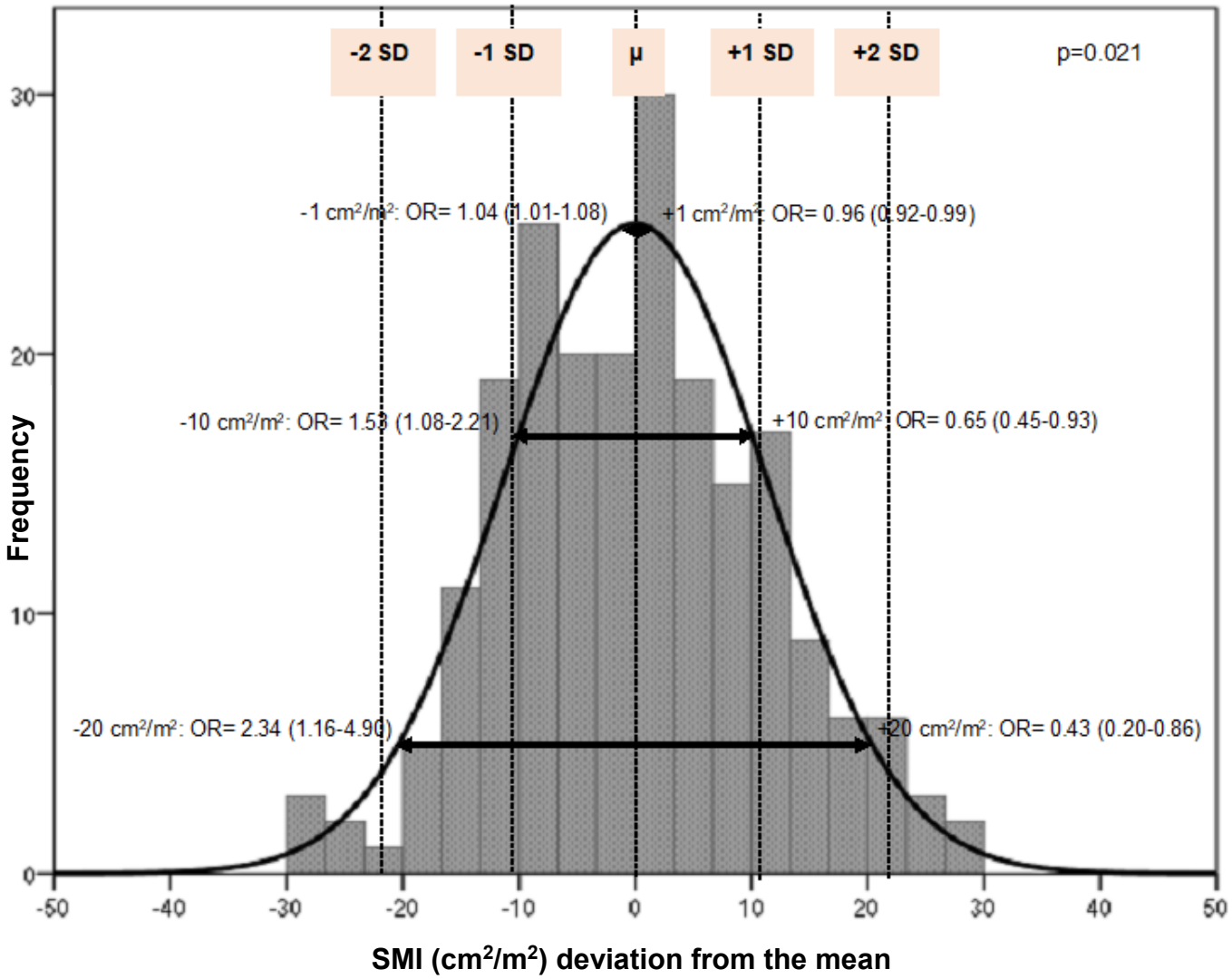
[a] Pooled T4 and L3 skeletal muscle index corrected for deviation from the mean; [b] Significance set at a 0.05 level

Table 3. continued

	Early termination of chemotherapy related to toxicity							
	Univariate (n=213)		Multivariate					
Covariables	**OR [95%CI]**	**p-value**	**AIC OR [95% CI]**	**p-value**	**BIC OR [95%CI]**	**p-value**	**SCAT OR [95%]**	**p-value**
ECOG performance status (0-1)								
2-4	1.12 [0.48-2.62]	0.791						
Co-morbidity (No)								
Yes	2.21 [1.16-4.21]	0.016[b]	2.38 [1.21-4.87]	0.015[b]	2.52 [1.30-5.07]	0.008[b]	2.49 [1.27-5.08]	0.010[b]
Alcohol drinking (No)								
Yes	0.69 [0.38-1.27]	0.235	1.80 [0.58-5.80]	0.314				
Smoking (No)								
Yes	0.92 [0.49-1.72]	0.802	1.50 [0.77-3.01]	0.243				
Alcohol AND smoking (No)								
Yes	0.69 [0.48-1.01]	0.055	0.41 [0.17-0.97]	0.044[b]			0.66 [0.44-0.98]	0.044[b]

[a] Pooled T4 and L3 skeletal muscle index corrected for deviation from the mean; [b] Significance set at a 0.05 level

Figure 1

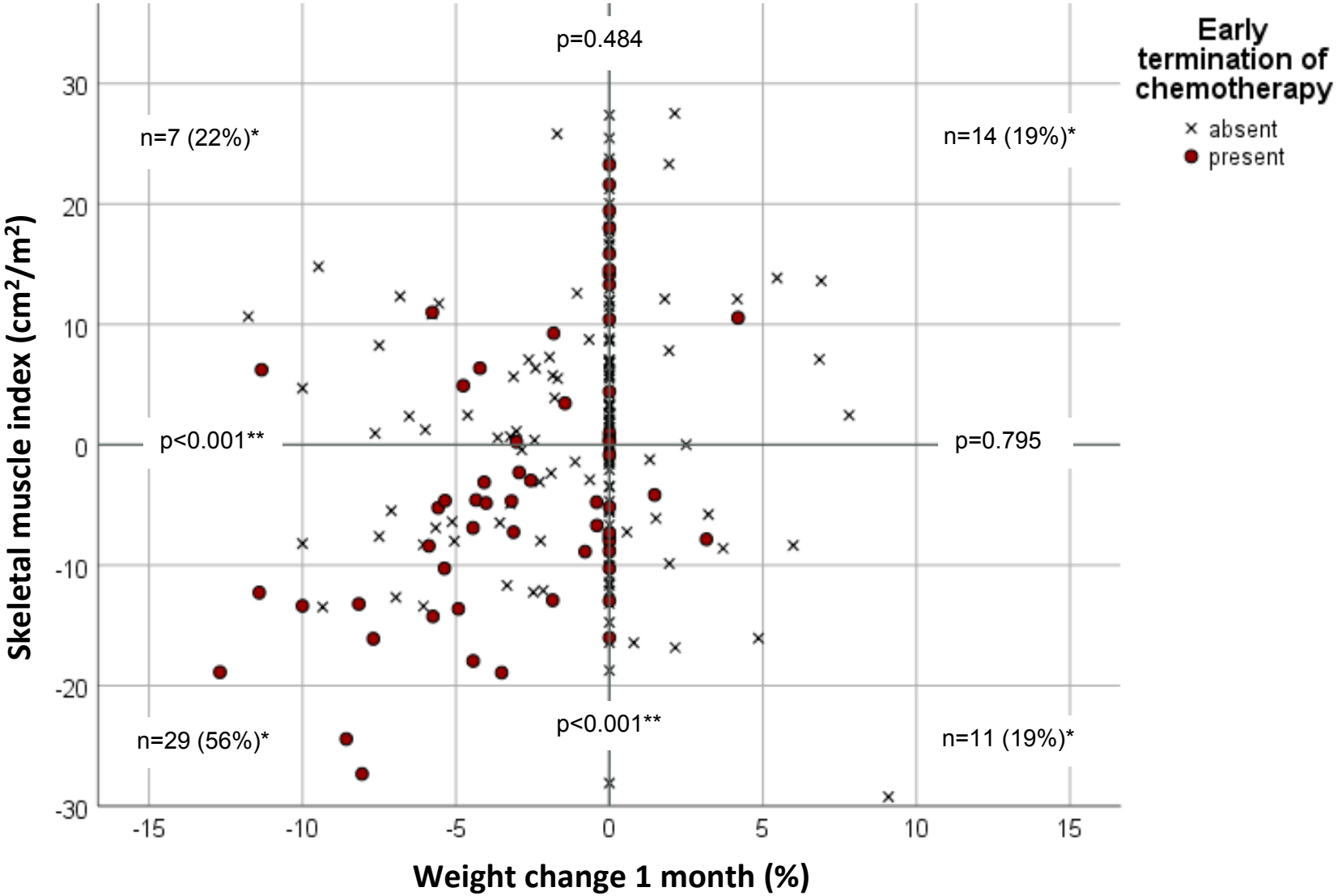


Magnitude of toxicity related unplanned early termination of chemotherapy is assessed with SCAD analysis of skeletal muscle index (SMI; cm^2/m^2). Positive deviation from the group mean is associated with decrease of the odds of early termination: an SMI that is 1 cm^2/m^2 higher indicates a decrease in odds of early termination of 4% (OR=0.96). An SMI that is 20 cm^2/m^2 higher indicates a decrease in odds of early termination of 57% (OR=0.43). Accordingly, negative deviation from the group mean is associated with an increase of the odds for early termination: an SMI that is 1 cm^2/m^2 lower indicates an increase of odds of early termination of 4% (OR=1.04). An SMI that is 20 cm^2/m^2 lower indicates an increase of odds of early termination of 134% (OR=2.34).

SMI deviation to the mean (cm^2/m^2)	Corresponding lumbar or thoracic SMI (cm^2/m^2)		OR of early termination of chemotherapy (95% CI)
	lumbar	**thoracic**	
+20	71.6	85.5	0.43 (0.20-0.86)
+10	61.6	75.5	0.65 (0.45-0.93)
+1	52.6	66.5	0.96 (0.92-0.99)
0	51.6	65.5	1.00
-1	50.6	64.5	1.04 (1.01-1.08)
-10	41.6	55.5	1.53 (1.08-2.21)
-20	31.6	45.5	2.34 (1.16-4.90)

Figure 1. Associated odds of early termination of chemotherapy treatment for skeletal muscle index (SMI; cm^2/m^2) in patients with head and neck cancer

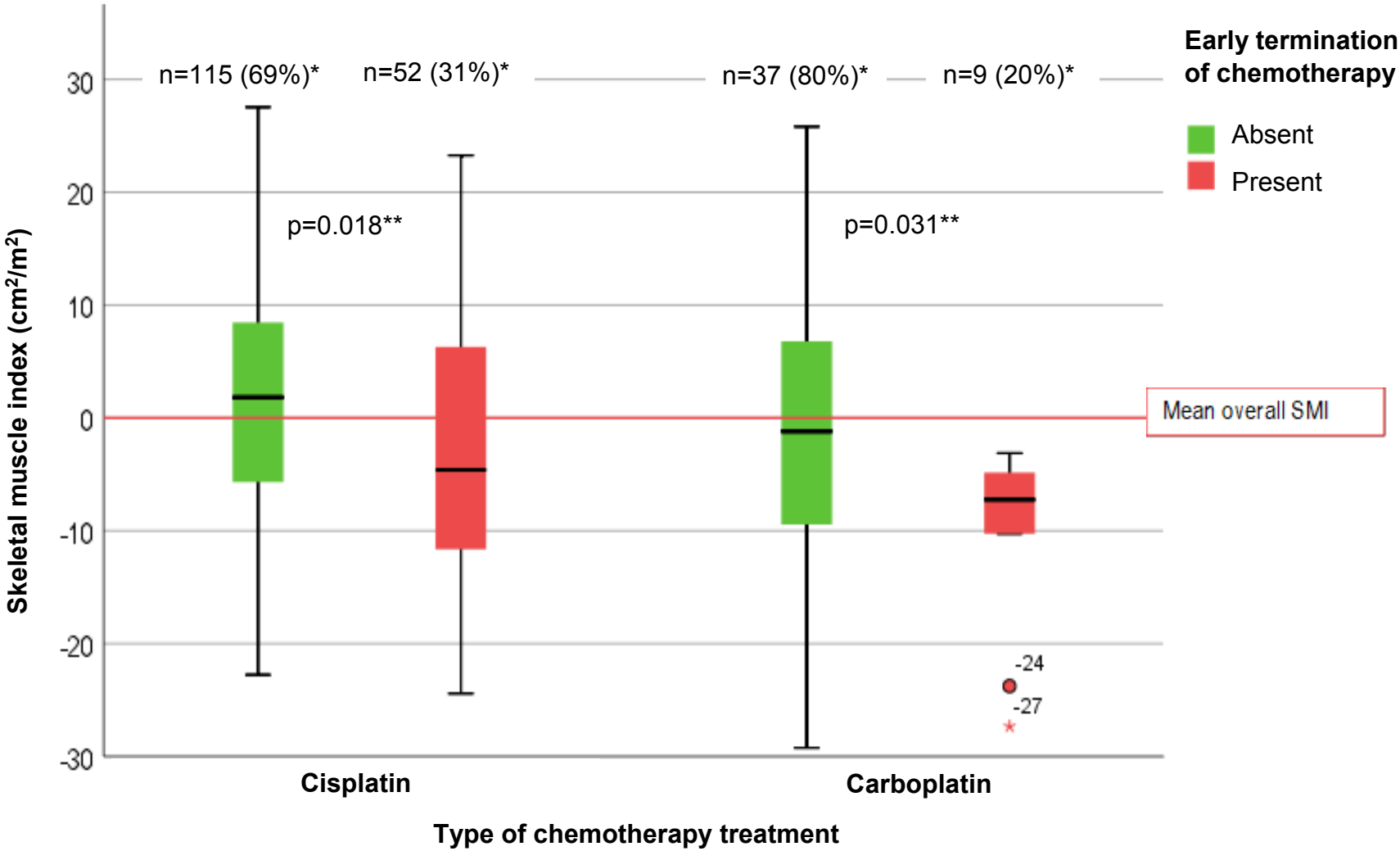
Figure 2



*n patients with early termination present; p-values calculated with Fisher's exact test;
**significance assumed at p<0.05

Figure 2. Distribution of 1 month weight loss percentage across absence (cross) or presence (circle) for early termination of chemotherapy for skeletal muscle index corrected for deviation of the mean (SMI: cm2/m2) in patients with head and neck cancer.

Figure 3



* Number (%) of patients with early termination absent or present.

** Difference in distribution of SMI (cm^2/m^2) across early termination absent or present for cisplatin and carboplatin was tested with an independent samples Mann-Whitney U test. Significance was set at 0.05.

Figure 3. Distribution of skeletal muscle index corrected for deviation from the mean (SMI: cm^2/m^2) across absence (left) or presence (right) of early termination of chemotherapy for cisplatin-based and carboplatin-based treatment in patients with head and neck cancer.